PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

REPLY TO:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

DUE ON MAR 09 2005

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2004/000697	07.05.2004	09.05.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/40

Applicant
TRANSFERT PLUS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later. FEB 5/c MAR 9/05

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-17,20,21,27-31,36-38,40-46 (all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-17,20,21,27-31,36-38,40-46 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-54
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-3,8,9,18-21,23,28,30,31,42-54
	No:	Claims	4-7,10-17,22,24-27,29,32-41
Industrial applicability (IA)	Yes:	Claims	18,19,22-26,32-35,39,47-54
	No:	Claims	1-17,20,21,27-31,36-38,40-46: Opinion reserved

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

The application concerns the therapeutic application of melanotransferrin, also known as MTf or p97. The Applicant has uncovered the molecular mechanism by which this protein acts in angiogenesis and makes use of this in approaching a number of clinical problems.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 **Claims 1-17,20,21,27-31,36-38,40-46** are all considered to directly or covertly constitute methods of treatment. No unified criteria exist in the PCT Contracting States on the question whether methods of treatment are industrially applicable, as they are not considered to be industrially applicable in the EPC. No opinion can be given, therefore, on the industrial applicability of these claims.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: SALA ROBERTA ET AL: "The human melanoma associated protein melanotransferrin promotes endothelial cell migration and angiogenesis in vivo." EUROPEAN JOURNAL OF CELL BIOLOGY, vol. 81, no. 11, November 2002 (2002-11), pages 599-607, XP002300166 ISSN: 0171-9335

D2: US-B-6 455 4941 (JEFFERIES WILFRED A ET AL) 24 September 2002 (2002-09-24)

D3: DEMEULE MICHEL ET AL: "Regulation of plasminogen activation: A role for melanotransferrin (p97) in cell migration." BLOOD, vol. 102, no. 5, 1 September 2003 (2003-09-01), pages 1723-1731, XP002300165 ISSN: 0006-4971

D4: US 2002/119095 A1 (BROOKS ROBERT CHARLES ET AL) 29 August 2002 (2002-08-29)

V.2 **Novelty - Art.33(1) and (2) PCT:**

V.2.1 The prior art identifies p97 and antibodies directed thereto as being useful as a delivery protein or as a pro-angiogenic factor, and diagnostic applications respectively. None of the cited documents, however, discloses the physiological role of p97 now attributed to it by the Applicants and so these documents are not considered to disclose the claimed subject matter.

V.3 **Inventive Step - Art.33(1) and (3) PCT:**

V.3.1 In direct contradiction of the application, D1 teaches that p97 is a pro-angiogenic factor, stimulating and not inhibiting cell migration. The closing sentence of the application suggests that "[l]imiting the pro-angiogenic activity of MTf may therefore provide a method to decrease the vascularisation of tumours and therefore limit tumour progression or growth". Confronted with this suggestion, the skilled person would look for available potential p97 antagonists. Antibodies are well known in the art for their occasional agonistic as well as antagonistic activity by virtue of their binding to ligand binding sites and either mimicking the ligand or allostearically preventing the ligand from binding a given receptor.

V.3.2 The prior art is awash with references to anti-p97 antibodies (see particularly cited passages of D2 and D4). The IPEA submits that it would be obvious to the skilled person to investigate whether or not the known antibodies possess the highly desirable anti-angiogenic properties proposed in D1 and thus inventive step cannot be acknowledged for claims pertaining to the inhibition of cell migration and angiogenesis (**claims 4-7,10-17,22,24-27,29,32-41**).

V.3.3 It is noted that D1 cannot be considered to fairly suggest that p97 promotes plasminogen activation or fibrinolysis.

V.5 Requirements for any Amendments Art. 34(2)(b) PCT:

V.4.1 Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

V.4.2 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

Re Item VII

Certain defects in the international observation

VII.1 D1 contradicts the application in that it identifies soluble p97 as promoting cell migration and angiogenesis. The only plausible way to explain the contradictory effects of p97 in the two documents is that the activity of p97 is in some way dependent on the environment, be it the cell type or the experimental conditions. Because the claimed effects of p97 are obviously not universal, the claims should be limited to indicate the conditions under which the purported activity stands, insofar as this is permitted within the scope of the application as filed. Other subject matter is considered to offend the support requirements of Articles 5 and 6 PCT.

VII.2 The Applicants have shown that the monoclonal antibody L235 interacts with p97 in a way that modifies the activity of the protein. However, it cannot be expected that other mAbs have the same effect as they will have distinct binding sites. The Applicants have not demonstrated that any of the other claimed antibodies have a similar desired effect to that of L235. Claims directed to either undisclosed antibodies or antibodies other than L235 should be restricted in scope to L235 in order to ensure that the claimed subject matter is properly supported (Article 6 PCT).